REMARKS

By way of this Amendment, Applicant has cancelled all pending claims 1-25 and has introduced new claims 26-38 which, like claims 18-25 that were elected for prosecution on the merits, are directed to oligonucleotides containing at least one detectable label. Thus, Applicants respectfully submit that the new claims are "consonant" with the restriction requirement set forth in Paper No. 4. Support for the two independent claims 28 and 33 is set forth in paragraphs 11 and 12 in the specification. Recitations of the dependent claims are contained in claims 24 and 25 as well as throughout the specification. Thus, no new matter has been added. In view of the foregoing, entry of the Amendment is respectfully requested.

Applicants submit that the new claims serve to overcome all grounds of rejection set forth under 35 U.S.C. §112, second paragraph. Reconsideration and withdrawal of the rejection are respectfully requested.

Claim 18 was rejected under §102 (b) as being anticipated by Biolabs product numbers 1317-1321, page 97, 1993/1994, and its teaching of an oligo $d(T)_{36}$ having the formula $T(T)_{34}T$. Claim 18 has been cancelled. The disclosed oligo does not contain a nucleotide repeat region containing at least one detectably labeled nucleotide and a plurality of nucleotides that are not detectably labeled. Thus, the publication does not anticipate claims 26-38. Reconsideration and withdrawal of the rejection are respectfully requested.

Claims 18-20 were rejected as being anticipated by U.S. Patent 5,403,708 to Brennan (hereinafter "*Brennan*"). The Examiner has alleged that *Brennan* discloses the preparation of an oligonucleotide comprising a labeled ligation product having different lengths which differ by N nucleotide residues or a

multiple thereof, and that the detection of the relative position and the type of label in this sequence in the nucleotide residues in the heterogeneous ligation product is generally determined by size separating the ligating product coupled with detection of the type of label incorporated in each ligation product of a specific size. Since claims 18-20 have been cancelled, the rejection is believed to be moot. Applicant also submits that *Brennan* does not anticipate claims 26-38. All of the oligos in *Brennan's* oligos would not be the same.

The disclosure on column 5, lines 50-54, of *Brennan* reads as follows:

> However, as indicated in an alternate embodiment such extension oligonucleotides can contain a differentially labeled sequencing nucleotide residue at a predetermined position to provide sequencing information.

In a subsequent passage of the disclosure, *Brennan* elaborates on this alternate embodiment on the basis of this teaching. It is plain that *Brennan's* intent is to create a population of ligation products which when annealed to the target nucleotide sequence in succession will result in each target nucleotide residue being base paired with a labeled nucleotide residue in a ligation product. In this fashion, the target sequence is determined thusly:

> In an alternate embodiment, the labeled nucleotide residue is not contained within the terminating moiety but rather is contained within the extension oligonucleotide. When so used, the extension oligonucleotide is sometimes referred to as a sequencing oligonucleotide. When so used, the sequencing nucleotide residue is located at a predetermined nucleotide position in a manner analogous for that set forth in FIG. 4 for a terminating moiety. However, in this

> embodiment, the oligonucleotide does not contain a chain-terminating nucleotide. When such sequencing oligonucleotides are used as an extension oligonucleotide, the ligation product so formed contains one or more labeled nucleotide residues in each molecule of the ligation product formed. Further, since the sequencing nucleotide is located at a predetermined nucleotide position, each of the labeled sequencing nucleotide residues in the ligation product are separated by N-nucleotides. As with the previous embodiment, these labeled nucleotide residues are base paired with nucleotide residues in the nucleic acid template that comprise a set of target nucleotide residues defining a particular reading frame. As with the previous embodiment, the reading frame can be shifted by varying the terminal nucleotide residue in the ligation primer or the predetermined nucleotide position containing the labeled nucleotide residue. FIG 5 sets forth the ligation product formed in this embodiment of the invention wherein the terminal nucleotide of the ligation primer is varied as between LP1, LP2 and LP3 and the labeled nucleotide is kept constant. In essence, the same sequence information is contained in each of the reaction products but is manifested in a different physical form. As such, the detection of the relative position of each of the labeled sequencing nucleotide residues and the label associated with each of those nucleotides is determined in a manner different from that of the previous embodiment.

Brennan, on column 9, lines 11-47. *Brennan's* intent is to create a population of ligation products which when annealed to the target nucleotide sequence in succession results in each target nucleotide residue being base paired with a labeled nucleotide residue in a ligation product. In this fashion, the target sequence is determined.

Persons skilled in the art would appreciate that the labeled A, T, C and G nucleotides in the ligation product population must each be conjugated to a different fluor in order to obtain meaningful sequencing information. This is exactly what *Brennan* teaches in practicing this alternate embodiment:

> In this regard, references is made to FIG. 6 which depicts a ligation product containing labeled nucleotide residues separated by an interval of four nucleotide residues. Label F2 is associated with cytosine nucleotide residues whereas label F3 is associate with guanidine nucleotide residues and label F4 is associated with thymidine nucleotide residues. As can be seen, the 5' end of the ligation product is immobilized. Such immobilization is readily obtained by utilizing a terminating moiety in the reaction mixture that contains one of the members of a binding pair covalently attached thereto. In this approach, it is preferred that the terminating moiety be added after the addition of sequencing oligonucleotide to the primed template so as to maximize the concentration and length of ligation product formed. After the covalent incorporation of the terminating moiety into the ligation product and denaturation, the labeled ligation product is contacted with a support containing the other member of the binding pair utilized in the terminating moiety. This provides not only for the separation of the labeled ligation product from the rest of the components of the reaction mixture but also allows for the determination of one or more of the nucleotide residues in a particular set of target nucleotides in the nucleic acid template.
>
> In the case of single molecule sequencing, (See Keller, supra), the labeled positions in the ligation product have a defined offset relative to the ligation primer. Therefore, as shown in FIG. 6, each ligation product has the same sequence

> commencing at its 3' end. As a consequence, an exonuclease can be contacted with the immobilized ligation product such that the exonuclease digestion of the immobilized ligation product is synchronized. When coupled to an appropriate flow cell detector for the labels employed, the relative order and type of label contained in the ligation product can be determined and the sequence of the target nucleotides in the nucleic acid ascertained.

Brennan, column 9, line 48, through column 10, line 17.

Plainly, *Brennan's* multiply labeled oligos described in the so-called alternate embodiment are different from the claimed oligonucleotides because they contain multiple fluors. That is, all the labels are not the same. Accordingly, the proper conclusion is that *Brennan* does not teach the claimed invention. Reconsideration and withdrawal of the rejection are respectfully requested.

Claims 18-25 have been rejected under 103 as obvious over Brennan. The Examiner has concluded that it would have been obvious to one skilled in the art to utilize ^{32}P or fluorophores as labels to prepare oligonucleotides having different sequence residues as disclosed in *Brennan* for use in obtaining information on the sequence of a nucleotide of interest. The Examiner explains that in such sequencing methods, the labeled ligation product provides information concerning the nucleotide residues in the nucleic acid template with which the labeled nucleotide residue is base paired (*Brennan*, columns 2-3). Since claims 18-25 have been cancelled, the rejection is believed to be moot. In view of the reasons that follow, Applicant also submits that the teachings of *Brennan* would not have rendered claims 26-38 obvious.

Brennan does not make any suggestion with respect to using his SO-containing ligation products for purposes other

than sequencing (that as explained above, would necessitate one fluorescent moiety). In addition, persons skilled in the art would realize that oligonucleotides labeled with only one dye moiety would be useless in *Brennan's* sequencing scheme because they would not yield meaningful sequencing information. Thus, the modification would not make sense from a technical standpoint because it would result in an inoperable process. This being the case, it is improper from a legal standpoint to interpret *Brennan* so as to be suggestive of modifying the SO-containing ligation products to contain only one detectable label. See, e.g., *In re Gordon*, 221 U.S.P.Q. 1125, 1127 (Fed. Cir. 1984) (reversing the Board's conclusion of *prima facie* obviousness) ("The mere fact that the prior art could be so modified would not have made the modification obvious unless the prior art suggested the desirability of the modification...Indeed, if the French [prior art] apparatus were turned upside down, it would be rendered inoperable for its intended purpose.").

In view of the foregoing, reconsideration and withdrawal of the rejection are respectfully requested.

As it is believed that all of the rejections set forth in the Official Action have been fully met, favorable reconsideration and allowance are earnestly solicited.

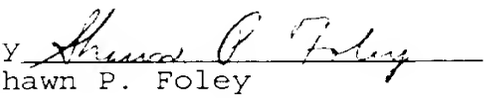
Attached hereto is a marked-up version of the changes made to the claims by the current amendment. The attached page is captioned "**Version with markings to show changes made**".

If, however, for any reason the Examiner does not believe that such action can be taken at this time, it is respectfully requested that he telephone applicant's attorney at (908) 654-5000 in order to overcome any additional objections which he might have.

If there are any additional charges in connection with this requested amendment, the Examiner is authorized to charge Deposit Account No. 12-1095 therefore.

Dated: April 14, 2003

Respectfully submitted,

By 

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